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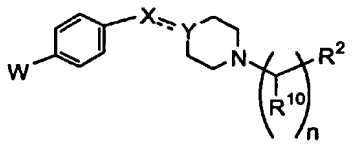
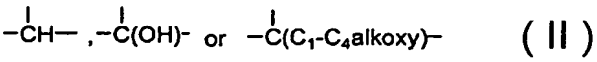
(54) Title: PIPERIDINE MCH ANTAGONISTS AND THEIR USE IN THE TREATMENT OF OBESITY



(I)



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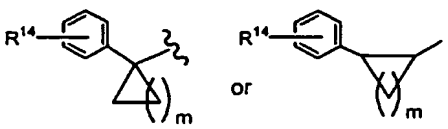

(III)

(57) Abstract: Disclosed are compounds represented by structural formula (I) or a pharmaceutically acceptable salt, ester or solvate thereof, wherein W is R^1-$CR^3R^{12}NR^4C(O)$- or $R^{11}C(O)NR^4$-; the dotted line is an optional double bond; X is CHR^8-, -C(O)-, or -C(=NOR^9)-; Y is (II); R^1 is optionally substituted cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkyl-alkyl; R^2 is optionally substituted aryl or heteroaryl; R^3 is alkyl, aryl or heteroaryl; R^4 and R^{12} are H or alkyl; R^8 is H, alkyl or alkoxyalkyl; R^9 is H, alkyl or arylalkyl; R^{10} is H, alkyl or aryl; R^{11} is (III), or, when R^2 is R^6-heteroaryl or R^{10} is not H, R^{11} can also be R^5-phenylalkyl; n is 1-3 and m is 1-5; and R^{14} is 1-3 substituents selected from H, alkyl, halogen, -OH, alkoxy and CF_3; and pharmaceutical compositions containing the compounds and methods of using the compounds in the treatment of eating disorders and diabetes.

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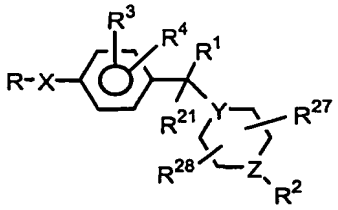
PIPERIDINE MCH ANTAGONISTS AND THEIR USE IN THE TREATMENT OF OBESITY

BACKGROUND OF THE INVENTION

This invention relates to amide derivatives of 1,4-di-substituted piperidine antagonists for melanin-concentrating hormone (MCH) and their use in the treatment of obesity and diabetes.

MCH, a cyclic peptide, was first identified over a decade ago in teleost fish where it appears to regulate color change. More recently, MCH has been the subject of investigation for its possible role as a regulator of eating behavior in mammals. As reported by Shimada et al., *Nature*, Vol. 396 (17 Dec. 1998), pp. 670-673, MCH-deficient mice have reduced body weight and leanness due to hypophagia (reduced feeding). In view of their findings, the authors have suggested that antagonists of MCH action may be effective for the treatment of obesity. U.S. Patent No. 5,908,830 discloses a combination therapy for the treatment of diabetes or obesity involving the administration of a metabolic rate increasing agent and a feeding behavior modifying agent, an example of the latter being an MCH antagonist.

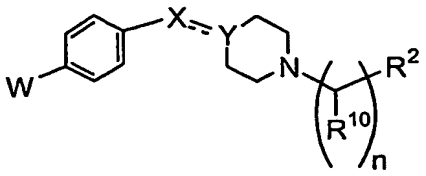
Piperidine-derivative muscarinic antagonists useful in the treatment of cognitive disorders such as Alzheimer's disease are disclosed in US 6,037,352. In particular, US 6,037,352 discloses compounds of the generic formula



wherein, inter alia, Y is CH; Z is N; X is -NHCO -; R is substituted benzyl or cycloalkylalkyl; R^1, R^{21}, R^3, R^4, R^{27} and R^{28} are each hydrogen; and R^2 is optionally substituted cycloalkyl or arylalkyl. US 6,037,352 does not disclose the use of the compounds for treating obesity or diabetes.

SUMMARY OF THE INVENTION

The present invention relates to compounds represented by structural formula I:



I

or a pharmaceutically acceptable salt, ester or solvate thereof, wherein

W is R^1-$CR^3R^{12}NR^4C(O)$- or $R^{11}C(O)NR^4$-;

the dotted line is an optional double bond;

X is $-CHR^8$-, -C(O)-, $-C(=NOR^9)$-, or, when the double bond is present, $-CR^8=$;

Y is

$-\overset{|}{C}H-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_1\text{-}C_4\text{alkoxy})-$, or, when the double bond is present, $-\overset{\|}{C}-$;

R^1 is R^5-$(C_3\text{-}C_8)$cycloalkyl, R^5-$(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl, R^5-aryl, R^5-aryl-$(C_1\text{-}C_6)$alkyl, R^5-heteroaryl, R^5-heteroaryl$(C_1\text{-}C_6)$alkyl, R^5-heterocycloalkyl or R^5-heterocycloalkyl$(C_1\text{-}C_6)$alkyl;

R^2 is R^6-aryl or R^6-heteroaryl;

n is 1, 2 or 3;

R^3 is $C_1\text{-}C_6$ alkyl, aryl or heteroaryl;

R^4 is H or $C_1\text{-}C_6$ alkyl;

R^5 is 1-4 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, $C_1\text{-}C_6$ alkoxy, $-CF_3$, $(C_1\text{-}C_6)$-alkoxycarbonyl, $-SO_2NHR^4$, $-C(O)NHR^4$, $-NR^4C(O)NHR^4$, $-NR^4C(O)R^4$, $-NR^4SO_2R^4$, R^{13}-phenyl and naphthyl;

R^6 is 1-4 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, -SH, -S($C_1\text{-}C_6$ alkyl), -CN, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkylcarboxy, CF_3, $-NO_2$, $-NH_2$, $(C_1\text{-}C_6)$alkylamino, phenyl, $(C_1\text{-}C_6)$-alkoxycarbonyl and R^7-phenoxy, or adjacent ring carbon atoms form a ring with the group $-O(CH_2)_{1\text{-}2}O$-, $-O(CH_2)_{2\text{-}3}$- or $-O(CF_2)O$-;

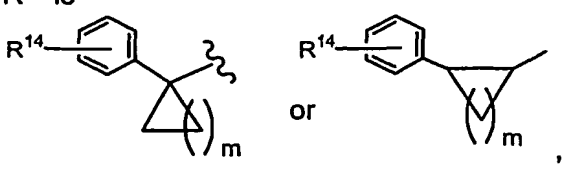
R^7 is 1-3 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, $C_1\text{-}C_6$ alkoxy and CF_3;

R^8 is H, $C_1\text{-}C_6$ alkyl or $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl;

R^9 is H, $C_1\text{-}C_6$ alkyl or aryl-$(C_1\text{-}C_4)$alkyl;

R^{10} is independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl and aryl;

R^{11} is



,

or, when R^2 is R^6-heteroaryl or R^{10} is not H, R^{11} can also be R^5-phenyl(C_0-C_2)alkyl;

m is 1, 2, 3, 4 or 5;

R^{12} is H or C_1-C_6 alkyl;

R^{13} is 1 to 3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, -OH, C_1-C_6 alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$ and $-C(O)CH_3$; and

R^{14} is 1-3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, -OH, C_1-C_6 alkoxy and CF_3.

The present invention also relates to a method of treating eating disorders, such as obesity and hyperphagia, and diabetes comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I.

Another aspect of the invention is a pharmaceutical composition for treating eating disorders and diabetes which comprises a compound of formula I in combination with a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

Referring to formula I, above, one group of preferred compounds is that wherein W is R^1-$CR^3R^{12}NR^4C(O)$-.

R^1 is preferably R^5-phenyl. R^5 is preferably H, halogen, C_1-C_6 alkyl or phenyl, more preferably halogen or phenyl.

Another group of preferred compounds is that wherein R^2 is R^6-aryl, especially when n is 1. More preferred is R^6-aryl wherein "aryl" is phenyl and R^6 is 1-2 substituents.

X is preferably $-CHR^8$ wherein R^8 is H and Y is CH, or X and Y form a double bond.

R^3 is preferably ethyl or methyl, and R^4 and R^{12} are each preferably H.

R^{10} is preferably H or $-CH_3$; when n is 2-5, preferably only one R^{10} is alkyl and the rest are hydrogen.

Except where stated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as to the "alkyl" portions of "alkoxy", etc.

"Alkyl" represents a straight or branched saturated hydrocarbon chain having the designated number of carbon atoms. Where the number of carbon atoms is not specified, 1 to 6 carbons are intended.

"Cycloalkyl" represents a saturated carbocyclic ring having 3 to 8 carbon atoms.

The term "heterocycloalkyl " refers to 4- to 7-membered saturated rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and $-NR^7$-, wherein R^7 is H or C_1-C_6 alkyl, and wherein the remaining ring

members are carbon. Where a heterocyclic ring comprises more than one heteroatom, no rings are formed where there are adjacent oxygen atoms, adjacent sulfur atoms, or three consecutive heteroatoms. Examples of heterocyclic rings are tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

Halogen represents fluoro, chloro, bromo or iodo.

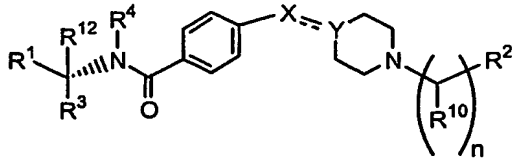
Aryl represents a monoaromatic ring or a bicyclic fused ring system of 6- to 10 carbon atoms, possessing one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, and the like.

Heteroaryl means a 5- to 10-membered single or benzofused aromatic ring comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N=, provided that the rings do not include adjacent oxygen and/or sulfur atoms. Examples of single ring heteroaryl groups are pyridyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazolyl. Examples of benzofused rings are indolyl, benzofuranyl, quinolyl, quinazolinyl, quinoxalinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, thianaphthenyl, and benzofurazanyl. N-oxides are also included. All positional isomers are contemplated, e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl.

When a variable appears more than once in the structural formula, for example R^5, the identity of each variable appearing more than once may be independently selected from the definition for that variable.

N-oxides can form on a tertiary nitrogen present in an R^1 or R^2 substituent, or on =N- in a heteroaryl ring substituent and are included in the compounds of formula I.

For compounds of the invention having at least one asymmetrical carbon atom, all isomers, including diastereomers, enantiomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of formula I. The preferred stereochemistry for compounds of the invention wherein W is R^1-$CR^3R^{12}NR^4C(O)$- is shown in formula IA:



IA

Compounds of formula I can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable

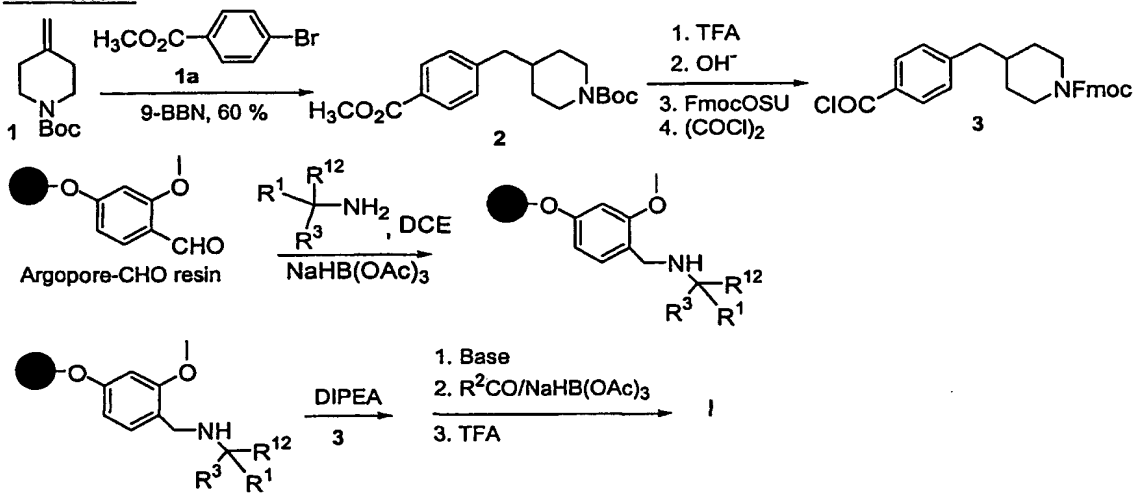
solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

Compounds of formula I can be produced by processes known to those skilled in the art using either solution phase or solid phase synthesis as shown in the following reaction schemes and in the preparations and examples below:

Compounds of Formula I wherein W is R^1-$CR^3R^{12}NR^4C(O)$- can be produced as shown in Scheme 1.

Scheme 1



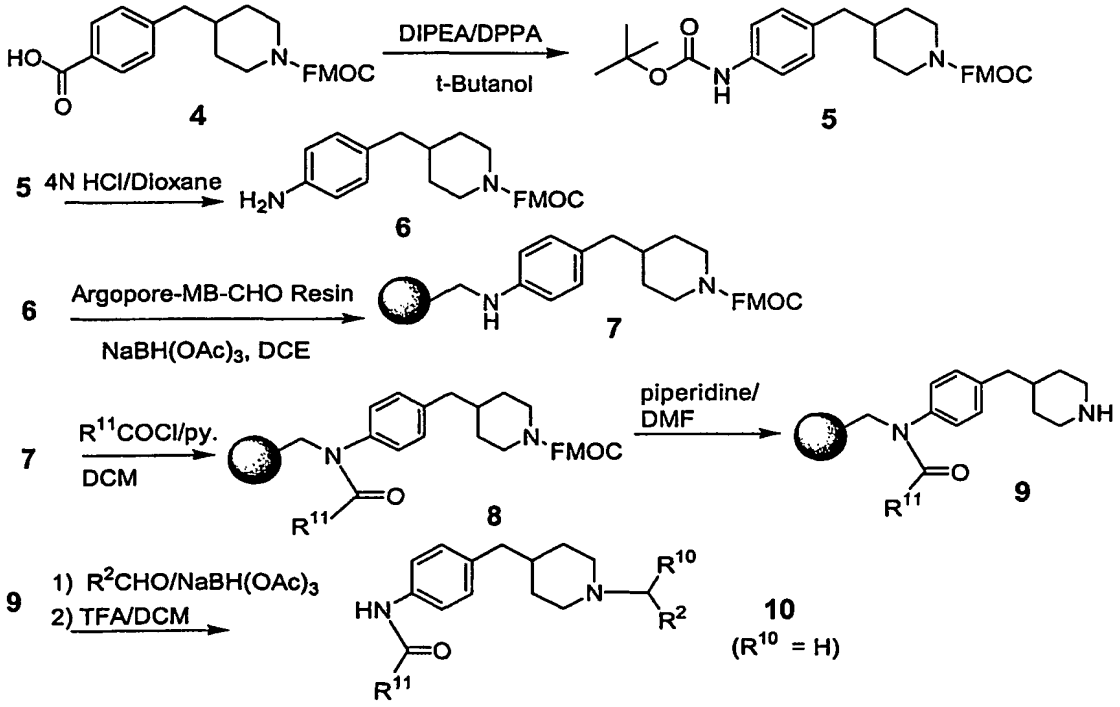
The synthesis of compounds such as **3** can be accomplished by the reaction of 9-borabicyclo[3.3.1]nonane (9-BBN) with an olefin such as **1** followed by the Suzuki coupling with an aryl halide such as **1a** to afford compounds **2**. Hydrolysis of ester **2** and subsequent deprotection of the N-Boc provides the amino acid intermediate which is protected by treatment with 9-fluorenylmethoxycarbonyl oxysuccinimide

(FmocOSU). This product is then converted into the acid chloride **3** upon treatment with reagents such as $POCl_3$ or oxalyl chloride.

The amine ($R^1CR^{12}R^3NR^5H$) is reacted with Argopore-MB-CHO resin (Argonaut Corporation, San Carlos, CA) by reductive alkylation with sodium triacetoxyborohydride. Subsequent acylation of the resin-bound amine with activated acids such as acid chlorides **3**, deprotection of the N-Fmoc group, followed by reductive alkylation with aldehydes or ketones, or reaction with an aldehyde followed by treatment with a Grignard reagent, or by reaction with the appropriate mesylate or alkyl halide, provides a resin bound intermediate, which on treatment with trifluoroacetic acid (TFA) produces compounds of Formula I.

Compounds of Formula I wherein W is $R^{11}C(O)NR^4$ can be prepared according to Scheme 2.

Scheme 2:

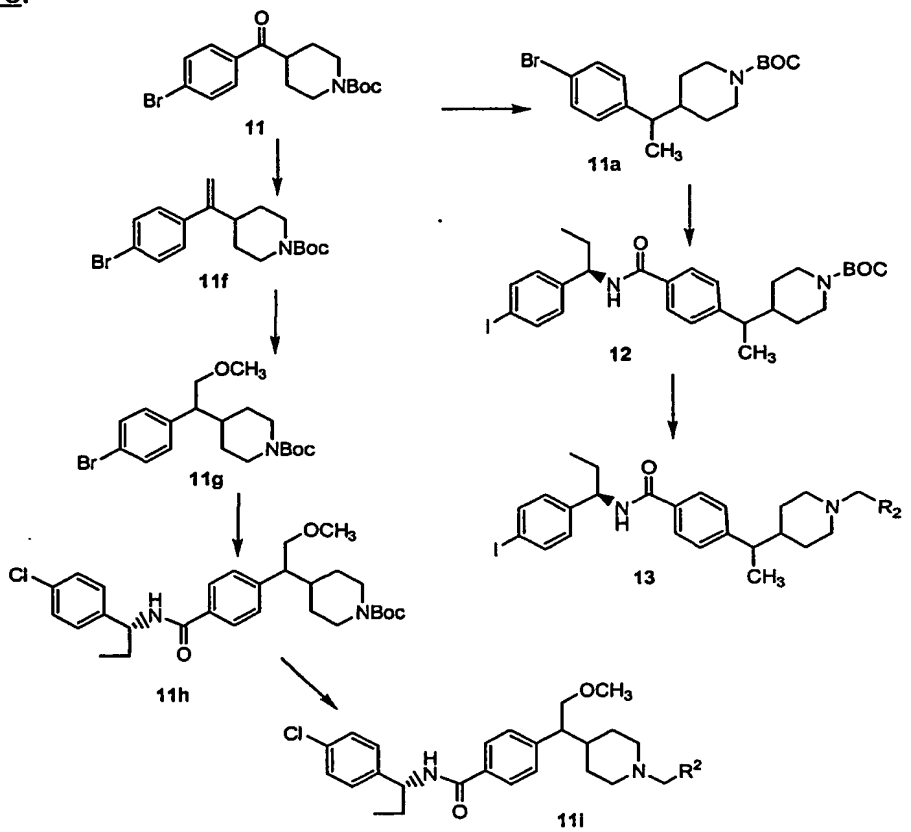


Compounds **10** can be prepared by the route shown in Scheme 2 by first converting an acid such as **4** into an amine such as **6** by the Curtius reaction, for example by treatment with diphenylphosphoryl azide in an alcohol such as t-butanol followed by hydrolysis. Subsequent reaction with a resin-bound aldehyde such as the Argopore MB-CHO resin under reducing conditions provides a resin-bound amine **7** which can be further functionalized by reaction with activated carboxylic acid derivatives such as acid chlorides. Removal of the FMOC group and reductive

alkylation with carbonyl-containing compounds, followed by treatment with acid to remove the compound from the polymeric resin, provides compounds **10**.

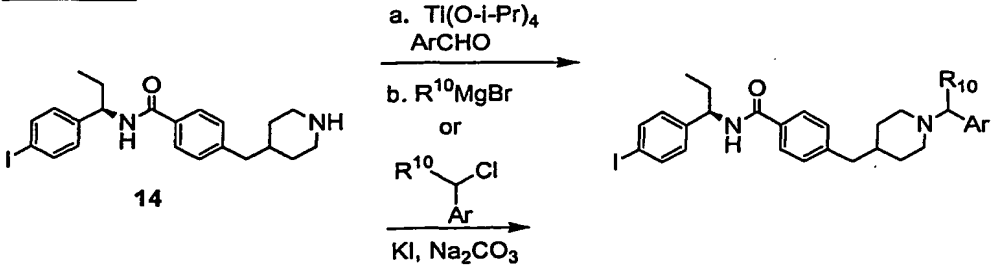
Alternatively, compounds of formula I are prepared as shown in Scheme 3 by reacting an aryl bromide such as **11a** with an alkyl lithium reagent, followed by addition of an aryl isocyanate. Subsequent removal of the BOC group from compound **12** by treatment with acid and then introduction of the R^2 group by alkylation or reductive alkylation provides compounds such as **13**. Furthermore, **11** can also be elaborated into compounds such as **11i** as shown in Scheme 3.

Scheme 3:



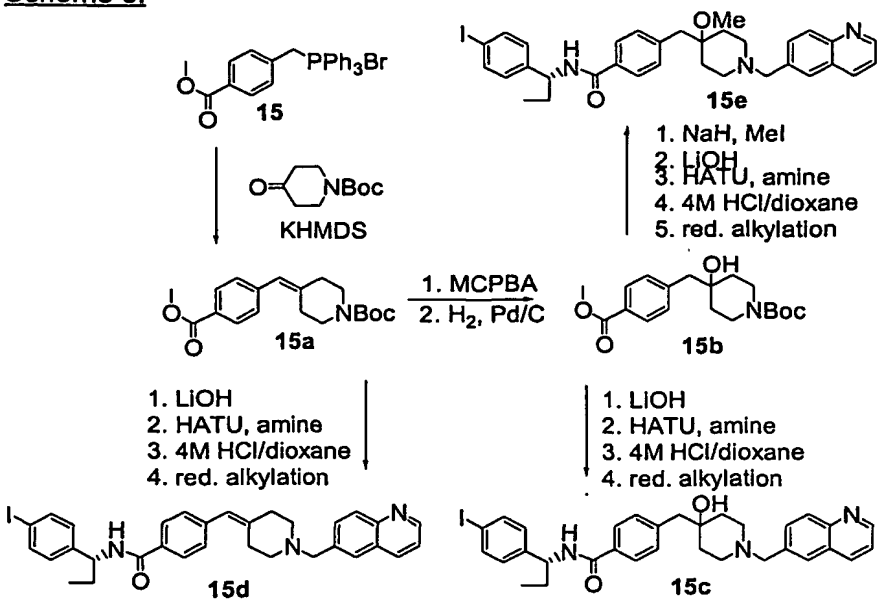
Compounds wherein R^{10} is alkyl can be prepared by the following procedure:

Scheme 4:

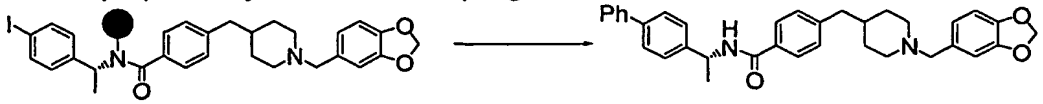


Additional compounds of formula I are prepared according the route shown in Scheme 5 (specific compounds are shown, but the procedure may be modified to make other compounds within the scope of formula I):

Scheme 5:



Compounds of formula I wherein W is R^1-$CR^3R^{12}NR^4C(O)$- and R^1 is biphenyl can be prepared by the Suzuki coupling reaction:



The iodophenyl analogs on Argopore-MB-CHO resin are treated with phenylboronic acid, K_2CO_3, $Pd(dppf)Cl_2$ and 1-methyl-2-pyrrolidinone. The resin is washed, then cleaved using 10% TFA/CH_2Cl_2.

Starting materials are prepared by known methods and/or methods described in the Preparations.

The compounds of formula I exhibit MCH receptor antagonizing activity, which has been correlated with pharmaceutical activity for treating eating disorders, such as obesity and hyperphagia, and diabetes.

The compounds of formula I display pharmacological activity in a test procedure designed to demonstrate MCH receptor antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses.
Following is a description of the test procedure.

MCH receptor binding assay

Membranes from CHO cells expressing the MCH receptor were prepared by lysing cells with 5 mM HEPES for 15 min at 4C. Cell lysates were centrifuged (12.5000 x g, 15 min) and the pellet was resuspended in 5 mM HEPES. For each 96-well plate (Microlite, Dynex Technologies), 1 mg of cell membranes were incubated with 10 mg of wheat germ agglutinin SPA beads (Amersham) for 5 min at 4 C in a volume of 10 ml of binding buffer (25 mM HEPES, 10 mM $MGCl_2$, 10 mM NaCl, 5 mM $MnCl_2$, 0.1% BSA). The membrane/bead mixture was centrifuged (1500 x g, 3.5 min), the supernatant was aspirated, and the pellet was resuspended in 10 ml binding buffer. The centrifugation, aspiration and resuspension were then repeated. The membrane/bead mixture (100 l) was then added to 96-well plates containing 50 l of 500 pM [^{125}I]-MCH (NEN) and 50 ml of the appropriate concentration of compound (4X the desired final concentration). Nonspecific binding was determined by including 1 M MCH in the binding reaction. The binding reaction was incubated at room temperature for 2 h. Plates were then analyzed in a TOPCOUNT microplate scintillation counter (Packard). Data was analyzed and Ki values were determined using GraphPad Prim.

For the compounds of this invention, a range of MCH receptor binding activity (Ki values) of from about 3 nM to about 1500 nM was observed. Compounds of this invention preferably have a binding activity in the range of from about 3 nM to about 500 nM, more preferably from about 3 to about 200 nM, and most preferably from about 3 to about 80 nM.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

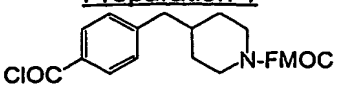
The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art. The following terms are abbreviated: room temperature (rt); ethyl acetate (EtOAc); tetrahydrofuran (THF); dimethylformamide (DMF); diisopropyl-ethylamine (DIPEA); and dichloroethane (EDC).

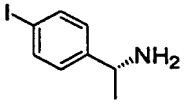
Preparation 1



See Scheme 1, above.

Mix starting material **1** (1 g) with 9-BBN (10.2 ml of a 0.5 M THF solution), place under a N_2 atmosphere and heat to reflux for 1 h. To the cooled solution add methyl 4- bromobenzoate (1.09 g), K_2CO_3 (0.84 g), $PdCl_2$(dppf) (0.21g), Ph_3As (0.155 g), DMF (7 ml) and water (1.1 ml) and heat at 65 °C for 3 h. Pour the reaction mixture into ice water, extract into EtOAc and purify the organic layer by flash chromatography (Hex: EtOAc (90:10) to yield compound **2** (1.1 g). Dissolve compound **2** (1.1 g) in CH_3OH (20 ml) and add LiOH (0.2g) and water (7.5 ml). After heating to reflux for 1 h, cool the reaction mix, remove the CH_3OH under vacuum and acidify the mixture with HCl. Collect the solid by filtration and dry in vacuo, and dissolve in 4 M HCl in dioxane (35 ml) and stir for 1.5 h. Add ether and collect the solid (0.67 g) by filtration. Add the solid (0.66 g) to a solution of Na_2CO_3 (0.6g) in water (120 ml) and dioxane (40 ml) followed by dropwise addition at 0 °C of a solution prepared from FMOC-OSuc (0.87g) and dioxane (10 ml). After 2 h at rt, remove the dioxane under vacuum and acidify the mixture with HCl. Collect the solid by filtration and dry in vacuo (0.93 g, LCMS 442.1[M+H]). Treat the residue with oxalyl chloride in CH_2Cl_2 to obtain the title compound.

Preparation 2



Step 1:

To a solution of (R)-α-methylbenzylamine (7.0 g, 57.8 mmol, 1 eq)/10 ml EDC was added trifluoroacetic anhydride (10 ml, 1.22 eq) in EDC (10 ml) below 30 ^{0}C. The mixture was stirred for 1.5 h and then cooled to 0 ^{0}C. Iodine (7 .0 g, 0.48 eq) was added, followed by addition of bis(trifluoroacetoxy)iodobenzene (12.6 g, 0.5 eq). The mixture was stirred overnight and quenched by 10 % $Na_2S_2O_3$ (130 ml). 130 ml CH_2Cl_2 was added and the organic layer was washed with saturated $NaHCO_3$. After drying over Na_2CO_3 and removing CH_2Cl_2, the solid was dissolved in ether (50 ml) by heat, followed by addition of hexane (150 ml). White solids were precipitated out and the mixture was further stirred for 2 h. Filtration afforded white crystal, which was washed with hexane (30 ml x 2) and air-dried. 9.2 g of the desired product was obtained in 46 % yield. ^{1}HNMR ($CDCl_3$): δ 1.6 (d, 3 H, J = 7.3 Hz), 5.08 (m, 1 H), 6.40 (br s, 1 H), 7.05 (d, 2 H, J = 8.3 Hz), 7.70 (d, 2 H, J = 8.3 Hz).

Step 2:

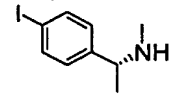
The product of step 1 (1 g, 2.91 mmol, 1 eq) was dissolved in CH_3OH (35 ml), water (10 ml) and 2N NaOH (6 ml). The solution was stirred overnight and TLC showed complete conversion. The solvent was removed and extraction with CH_2Cl_2 several times provided the desired product as colorless oil (0.69 g, 96 % yield).

^{1}HNMR ($CDCl_3$): δ 1.22 (d, 3 H, J = 6.5 Hz), 1.40 (s, 2 H), 3.98 (q, 1 H, J = 6.6 Hz), 7.00 (d, 2 H, J = 8.3 Hz)), 7.58 (d, 2 H, J = 8.3 Hz).

^{13}CNMR ($CDCl_3$): δ 27.12, 51.98, 93.09, 128.92, 138.36, 148.38.

HRMS for $C_8H_{11}IN$ (M + 1) calcd: 247.9936; found: 247.9936.

Preparation 3

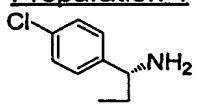


To a solution of the product of Preparation 2, step 1, (1 g, 2.92 mmol, 1 eq)/ 10 ml THF at 0 ^{0}C under N_2 was added KHMDS (0.5 M in toluene, 7 ml, 1.2 eq) dropwise. 20 min later, CH_3I (0.36 ml, 2 eq) was added and the mixture was stirred overnight. After workup and flash chromatography (EtOAc:hexane, 1:10), 1 g of the desired product was obtained. 2:1 rotamers were observed, the major one was reported as:

^{1}HNMR ($CDCl_3$): δ 1.58 (d, 3 H, J = 6.6 Hz), 2.80 (s, 3 H), 5.90 (q, 1 H, J = 6.6 Hz), 7.00 (d, 2 H, J = 8.3 Hz), 7.75 (d, 2 H, J = 8.3 Hz).

The above product was hydrolyzed in NaOH/CH_3OH to the amine in 85 % yield. ^{1}HNMR ($CDCl_3$: δ 1.30 (d, 3 H, J = 6.6 Hz), 1.40 (br s, 1 H), 2.30 (s, 3 H), 3.60 (q, 1 H, J = 6.6 Hz), 7.05 (d, 2 H, J = 8.3 Hz), 7.61 (d, 2 H, J = 8.3 Hz).

Preparation 4



4'-chloropropiophenone was reduced to (S)-4-chloro-α-ethylbenzyl alcohol according to *J.Org. Chem.* (1993), *58*, 2880-2888. (> 95 % ee by NMR of the corresponding Mosher's esters.)

^{1}HNMR ($CDCl_3$): δ 0.98 (t, 3 H, J = 7.4 Hz), 1.60-1.78 (m, 2 H), 1.80-2.00 (br s , 1 H), 4.58 (t, 1 H, J = 6.7 Hz), 7.22 (d, 2 H, J = 8.4 Hz), 7.30 (d, 2 H, J = 8.4 Hz).

The (S)-4-chloro-α-ethylbenzyl alcohol was then converted to the corresponding (R)-azide according to *J.Org. Chem.* (1993), *58*, 2880-2888.

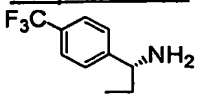
^{1}HNMR ($CDCl_3$): δ 0.98 (t, 3 H, J = 7.4 Hz), 1.70-1.85 (m, 2 H), 4.35 (t, 1 H, J = 6.7 Hz), 7.22 (d, 2 H, J = 8.4 Hz), 7.38 (d, 2 H, J = 8.4 Hz).

The azide was reduced by triphenylphosphine to the amine by literature procedures (*J. Med. Chem.* (1997), 2755-61).

^{1}HNMR ($CDCl_3$): δ 0.98 (t, 3 H, J = 7.3 Hz), 1.60 (m, 2 H), 3.75 (m, 1 H) 7.20 (m, 4 H).

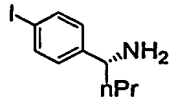
^{13}CNMR ($CDCl_3$): δ 12.08, 33.64, 58.35, 128.83, 129.43, 132.97, 133.33.

Preparation 5



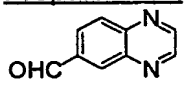
(R)-α-ethyl-4-trifluoromethylbenzylamine was prepared by methods similar to the above procedures. ^{1}HNMR ($CDCl_3$): δ 0.90 (t, 3 H, J = 7.4 Hz), 1.60-1.78 (m, 2 H), 2.00-2.18 (br s), 3.90 (t, 1 H, J = 6.9 Hz), 7.41 (d, 2 H, J = 8.2 Hz), 7.60 (d, 2 H, J = 8.2 Hz).

Preparation 6



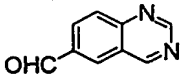
The title compound was prepared by a procedure similar to that described above. ^{1}HNMR ($CDCl_3$): δ 0.99 (t, 3 H, J = 7.3 Hz), 1.20-1.40 (m, 2 H), 1.50-1.70 (m, 4 H), 3.92 (t, 1 H, J = 6.9 Hz), 7.10 (d, 2 H, J = 8.3 Hz), 7.60 (d, 2 H, J = 8.3 Hz).

Preparation 7



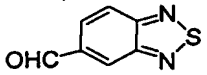
6-Methylquinoxaline was oxidized by SeO_2 to 6-formylquinoxaoline in > 80 % yield according to Chem. Abstr. (1945), *39*, 4077-4078.
^{1}HNMR ($CDCl_3$): δ 8.20 (m, 2 H), 8.59 (s, 1 H), 8.98 (s, 1 H), 10.22 (s, 1 H).

Preparation 8



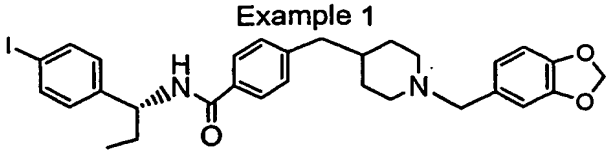
6-Methylquinazoline (prepared from 4-hydroxy-6-methylquinazoline according to *J. Am. Chem. Soc.* (1962) 561) was oxidized by SeO_2 to 6-formylquinazoline in 10 % yield. ^{1}HNMR ($CDCl_3$): δ 8.20 (d, 1 H, J = 8.3 Hz), 8.40 (d, 1 H, J = 8.3 Hz), 8.45 (s, 1 H), 9.40 (s, 1 H), 9.50 (s, 1 H), 10.20 (s, 1 H).

Preparation 9

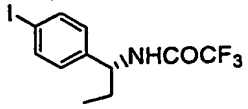


5-Methyl-2,1,3-benzothiadiazole was converted to the corresponding aldehyde according to the procedure of *Eur. J. Med. Chem.* (1993), 28, 141.
^{1}HNMR ($CDCL_3$) δ 8.10 (s, 2 H), 8.50 (s, 1 H), 10.20 (s, 1 H).

Example 1

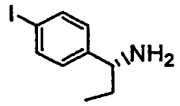


Step 1:



To (R)-α-ethylbenzylamine (19.8 g, 146.7 mmol, 1 eq) in EDC (30 ml) at 0 °C was added trifluoroacetic anhydride (25.3 ml, 1.22 eq) dropwise. The ice bath was removed and the mixture was stirred for 1.5 h. The crude was then cooled to 0 °C followed by the addition of I_2 (17.9 g, 0.48 eq) and bis(trifluoroacetoxy)iodobenzene (32.1 g, 0.51 eq). The dark purple mixture was stirred for 18 h until it became slightly yellow. 10 % $Na_2S_2O_3$ (330 ml) and CH_2Cl_2 (330 ml) were added and stirred at 0 °C for 0.5 h. After separation, the organic layer was washed with saturated $NaHCO_3$ until the pH of the aqueous layer was 9. After further extraction with CH_2Cl_2, the organic layers were combined and dried over Na_2CO_3. Removal of the solvent provided a white solid which was redissolved in CH_2Cl_2 (300 ml). The solution was treated with 1 liter of hexane and white solid precipitated. After filtration and washing with hexane and ether, 26.5 g of the desired product as white solid was obtained in 50 % yield.

Step 2:



The product of Step 1 (25 g) was dissolved in CH_3OH (200 ml), treated with 3 N NaOH (100 ml) at 0 °C and gradually warmed up to rt overnight. The solvent was removed and the solution was extracted with CH_2Cl_2 followed by drying with Na_2CO_3. After removal of the solvent, 14 g of the desired product was obtained in 77 % yield.

^{1}HNMR ($CDCl_3$): δ 0.82 (d, 3 H, J = 7.3 Hz), 1.46 (s, 2 H), 1.60 (m, 2 H), 3.78 (t, 1 H, J = 6.7 Hz), 7.05 (d, 2 H, J = 8.3 Hz), 7.60 (d, 2 H, J = 8.3 Hz).

^{13}CNMR ($CDCl_3$): δ 12.14, 33.60, 58.46, 93.10, 129.56, 138.35, 146.99.

HRMS for $C_9H_{13}IN$ (M + 1) calcd: 262.0093; found: 262.0092.

Elemental analysis: C, H, N. N: calcd: 5.36; found: 4.60.

Step 3:

The Argopore aldehyde resin (Argonaut Corporation, San Carlos, CA) (10 g, 0.76 mmol/g) in EDC (40 ml) was stirred with the product of Step 2 (7.93 g, 4 eq) for 15 min followed by addition of $NaB(OAc)_3H$ (6 g, 4 eq). The mixture was stirred under N_2 at rt for 20 h before being quenched with CH_3OH. The CH_3OH was removed and the crude was treated with 2N NH_3/CH_3OH for 0.5 h. The resin was further washed with CH_3OH, CH_2Cl_2 (3 times each) and dried under vacuum at 40 °C overnight.

Step 4:

The resin from Step 3 was treated with 10 eq of DIPEA and 2 eq of the product of Preparation 1 in CH_2Cl_2 at rt overnight. The resin was then washed with CH_2Cl_2 several times.

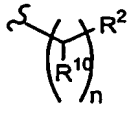
Step 5:

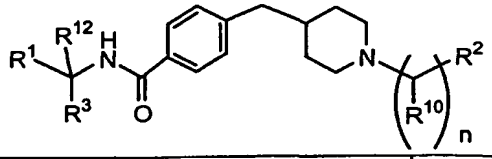
The resin of Step 4 was treated with 20 % piperidine/DMF for 1 h (twice). After washing with CH_2Cl_2, then EDC, the resin was treated with EDC, piperonal (10 eq) and $NaB(OAc)_3H$ (10 eq) under N_2 for 24-48 h. The resin was then washed with CH_3OH, 2N NH_3/ CH_3OH, CH_3OH, CH_2Cl_2 (3 times each) and dried under vacuum. Final cleavage was done with 10 % TFA/CH_2Cl_2 (1 h). The crude (TFA salt) was chromatographed to give the title compound (Rf = 0.45, CH_2Cl_2/CH_3OH/NH_4OH = 97/3/1).

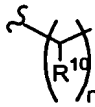
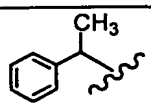
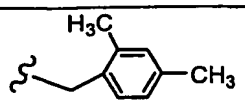
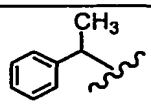
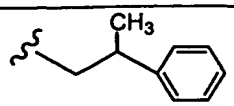
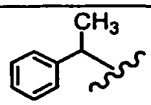
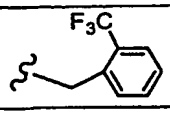
^1H NMR($CDCl_3$): δ 0.99 (t, 3 H, J = 7.3 Hz), 1.22-1.37 (m, 2 H), 1.45-1.60 (m, 3 H), 1.80-1.99 (m, 4 H), 2.58 (d, 2 H, J = 6.6 Hz), 2.82 (d, 2 H, J = 7.4 Hz), 3.40 (s, 2 H), 5.00 (q, 1 H, J = 7.4 Hz), 5.90 (s, 2 H), 6.25 (d, 1 H, J = 8.0 Hz), 6.70 (s, 2 H), 6.80 (s, 1 H), 7.10 (d, 2 H, J = 8.0 Hz), 7.18 (d, 2 H, J = 8.0 Hz), 7.65 (d, 4 H, J = 8.1Hz).

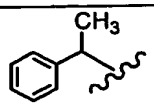
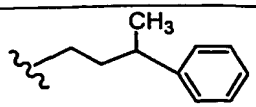
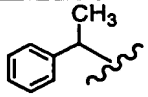
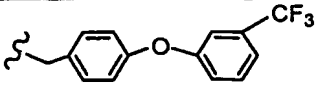
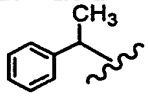
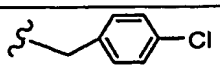
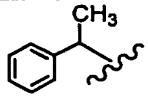
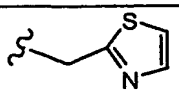
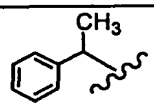
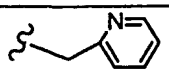
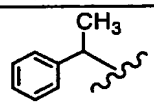
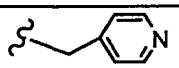
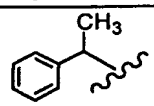
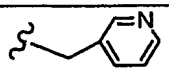
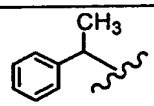
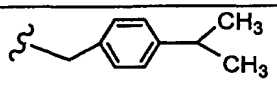
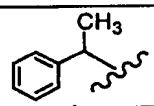
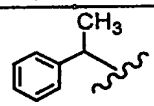
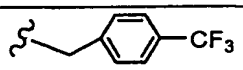
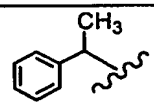
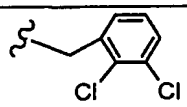
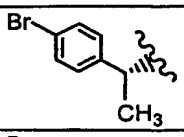
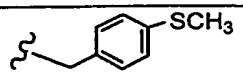
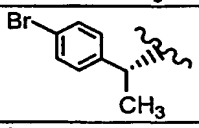
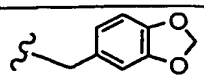
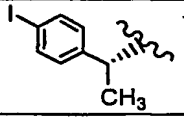
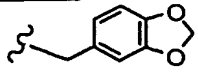
MS for $C_{30}H_{33}IN_2O_3$: 597 $(M+1)^+$

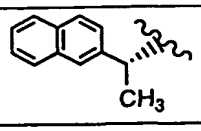
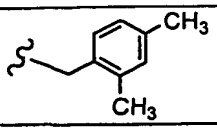
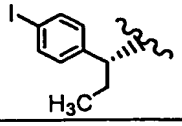
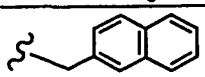
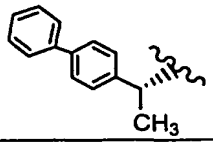
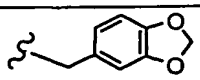
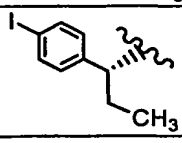
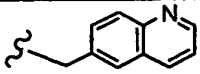
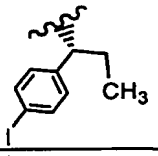
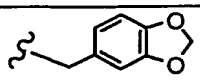
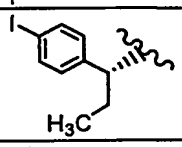
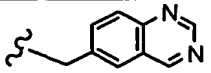
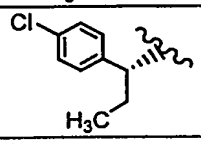
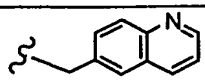
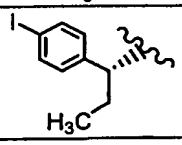
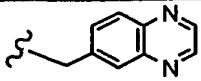
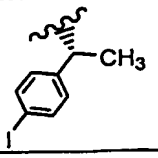
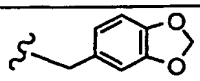
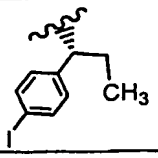
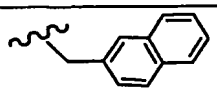
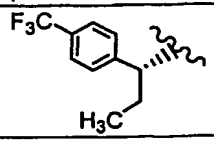
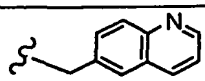
Tr = 6.7 min (gradient A (CH_3CN)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.)

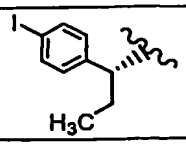
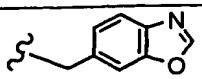
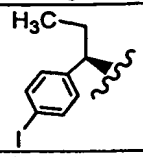
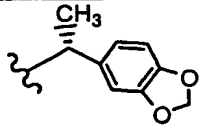
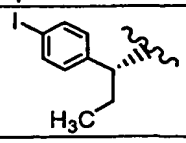
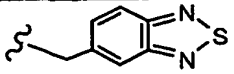
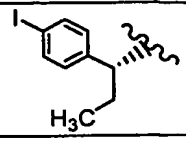
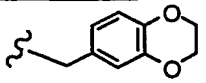
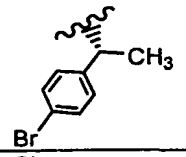
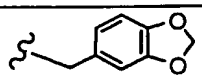
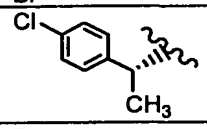
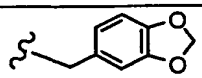
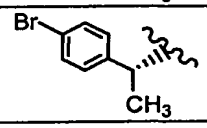
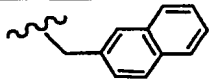
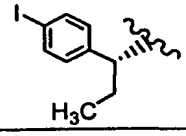
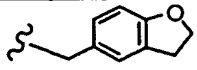
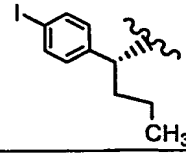
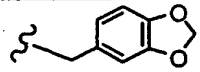
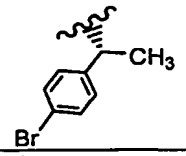
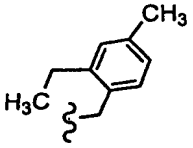
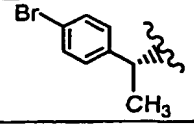
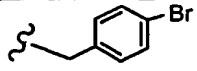
Using a similar procedure with the appropriate amines and aldehydes, the following compounds of formula I were prepared, wherein R^1-$CR^{12}R^3$- and  are as defined in the following Table 1:

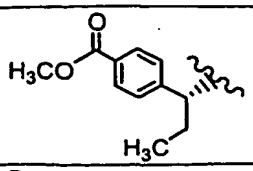
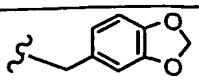
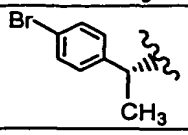
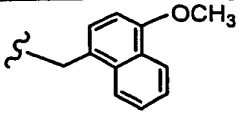
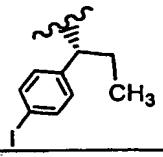
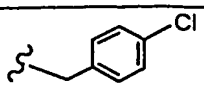
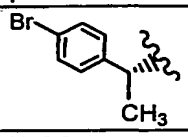
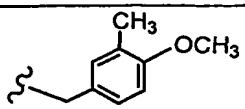
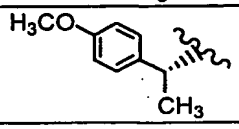
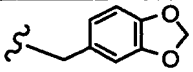
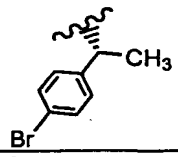
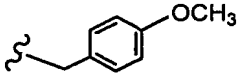
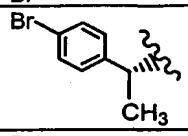
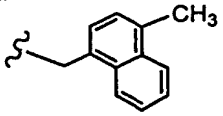
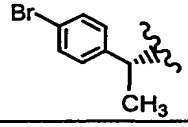
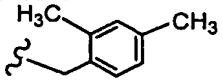
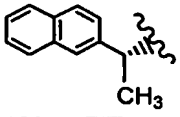
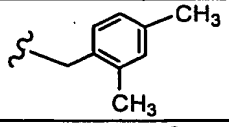
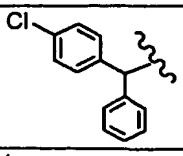
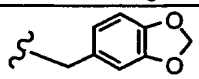
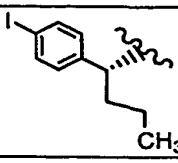
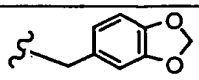


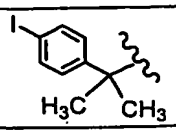
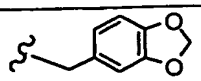
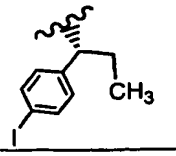
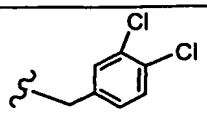
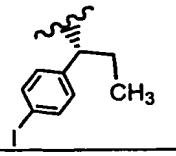
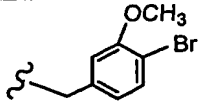
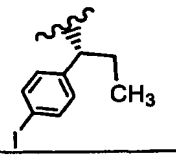
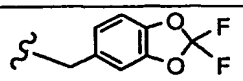
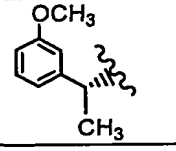
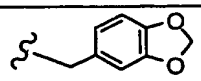
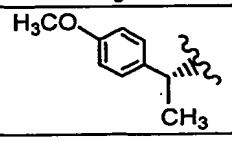
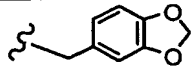
Ex.	R^1-$CR^{12}R^3$-		R_t (min.)	Obs. Mass
1-1			6.06	441.1
1-2			5.96	441.1
1-3			5.96	481.1

1-4			6.21	455.1
1-5			7.06	573.1
1-6			5.86	447.1
1-7			4.91	420.1
1-8			5.01	414.1
1-9			4.26	414.1
1-10			4.36	414.1
1-11			6.41	455.1
1-12			5.96	493.1
1-13			6.16	481.1
1-14			6.01	481.1
1-15			4.66	537
1-16			6.71	537
1-17			4.51	583

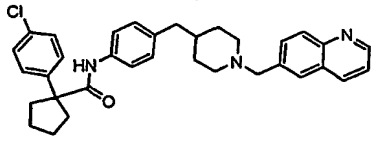
1-18			7.31	491
1-19			8.46	603
1-20			4.86	533
1-21			5.06	604.1
1-22			5.,36	597.1
1-23			4.91	605.1
1-24			7.16	512.1
1-25			5.21	605.1
1-26			4.51	583.1
1-27			8.46	603.1
1-28			7.46	546

1-29			5.16	594
1-30			5.01	611
1-31			5.31	611.1
1-32			8.61	611.1
1-33			6.66	535.1
1-34			4.91	491
1-35			4.71	541
1-36			4.31	595
1-37			5.36	611
1-38			7.21	519
1-39			4.51	571

1-40			7.26	529
1-41			4.71	571
1-42			8.26	587
1-43			4.66	535.1
1-44			4.61	487
1-45			6.81	521.1
1-46			4.86	555
1-47			4.65	519
1-48			7.31	491
1-49			5.31	553
1-50			5.36	611

1-51			5.21	597
1-52			8.51	621
1-53			8.11	663
1-54			8.41	633
1-55			4.85	487
1-56			4.82	487

Example 2



Step 1:

The acid **4** (4.42 g, 0.01 mol) is suspended in distilled t-butanol (30 ml), DIPEA (1.66 ml, 0.0095 mol) and diphenylphosphoryl azide (2.16 ml, 0.01 mol) are added under N_2, and the mixture is refluxed overnight. The t-butanol is removed by rotoevaporation, and the concentrated residue is purified by flash chromatography (EtOAc/Hexane (1:3) with 10% CH_2Cl_2), to obtain compound **5** (1.65 gm).

Step 2:

Compound **5** (2.85 g) is dissolved in 4N HCl in dioxane and stirred overnight, and concentrated. The residue is dissolved in 1N HCl, extracted with ether, and the HCl layer is basified with saturated $NaHCO_3$ solution to pH 9, and extracted with CH_2Cl_2 twice. The combined CH_2Cl_2 layer is washed with brine and dried over anhydrous Na_2SO_4, to give **6** (1.67 gm).

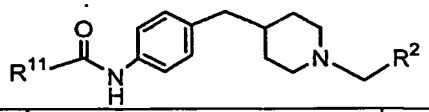
Step 3:

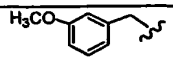
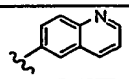
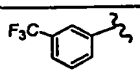
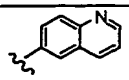
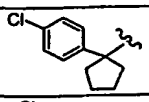
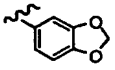
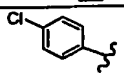
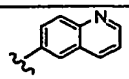
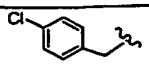
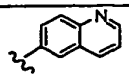
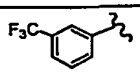
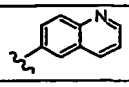
Argopore-MB-CHO resin (5.0 g, 0.76 mmol/g) is suspended in EDC (40 ml), amine **6** (1.67 g, 4.05 mmol) and $NaBH(OAc)_3$ (4.24 g, 20.25 mmol) is added and shaken for 70 h. CH_3OH is added, the reaction stirred for 30 min., then the resin is washed with 2N NH_3/CH_3OH (2x), CH_3OH (2x), THF (2x) and CH_2Cl_2 (2x), and dried under vacuum to obtain resin **7**.

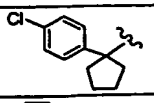
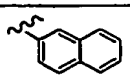
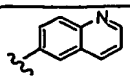
Step 4:

Resin **7** (70 mg, 0.76 mmol/g) is suspended in anhydrous CH_2Cl_2, then anhydrous pyridine (0.045 ml, 0.532 mmol) is added and mixed, followed by addition of 1-(4-chlorophenyl) 1-cycylopentanecarbonyl chloride (65 mg, 0.266 mmol). The mixture is shaken is overnight, then washed with CH_3OH (2x), THF (2x), CH_2Cl_2 (2x), and dried in vacuum to obtain resin bound amide. This resin is treated with 20% piperidine in DMF (3 times, 20 min each) then washed with THF (2x), CH_3OH (2x), CH_2Cl_2 (2x), and dried. The resultant resin is suspended in EDC, 6-quinoline carboxaldehyde (167 mg, 1.06 mmol) and $NaBH(OAc)_3$ (112.8 mg, 0.532 mmol) are added and the mixture is shaken for 70 h. The resin is washed with THF (2x), CH_3OH (2x), CH_2Cl_2 (2x), and treated with 40% TFA/CH_2Cl_2 for 30 min. The mixture is filtered and the volatiles are evaporated to obtain the title compound. LCMS Rt 7.69 min., observed mass 538.1 (M+H).

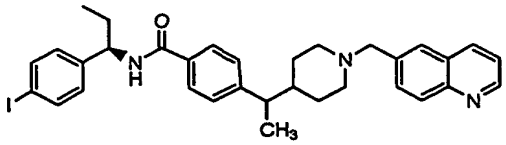
Using the same procedures with the appropriate acid chlorides and aldehydes the following compounds in Table 2 are obtained:



Ex.	R^{11}	R^2	R_t (min.)	Obs. Mass
2-1			6.54	480.1
2-2			7.21	504.1
2-3			8.76	531.1
2-4			6.89	470.1
2-5			7.21	484.1
2-6			7.51	504.1

2-7			9.09	537.1
2-8			7.29	476.1

Example 3



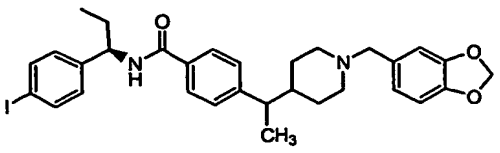
Step 1:

To a stirring solution of **11** (4 gm) in THF (20 ml) at –78 °C add CH_3MgBr (11 ml of a 3M solution in THF). After 30 min, warm to rt and then heat the reaction mixture at reflux temperature for 1 h and partition between saturated NH_4Cl and EtOAc. Wash the organic layers with 1N HCl and H_2O, dry over $MgSO_4$ and concentrate to dryness. Dissolve the residue (2.2 g) in CH_2Cl_2 (30 ml), add triethylsilane (15 ml) and TFA (15 ml). After stirring overnight, concentrate the reaction mixture under reduced vacuum (135 °C @ 2 mm Hg) to provide a yellow solid. Dissolve the solid (0.96 gm) in CH_2Cl_2 (30 ml), add $(BOC)_2O$ (1.6 g) and 1 N NaOH (20 ml). After 2 h, separate the organic layer, wash with 1 N HCl, and dry over $MgSO_4$. Concentrate the mixture under reduced pressure (1 mm Hg, 100 °C) to provide compound **11A** as light yellow oil (1.14 g).

Step 2:

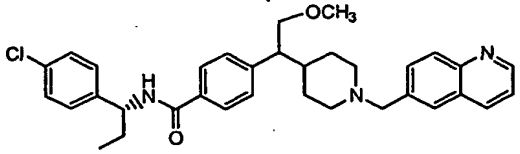
To a solution of **11A** (0.37 gm) in THF (10 ml) cooled to –78 °C, add n-BuLi (0.6 ml of a 2.5 M solution in hexane) with stirring. After 30 min at – 78 °C,add a solution of 1-(4-iodophenyl)-propylisocyanate (prepare this from R-α-ethyl-4-iodo-benzylamine from example 1, step 2, by reaction with triphosgene and proton sponge). After 15 min. add a solution of NH_4Cl and partition with CH_2Cl_2. The CH_2Cl_2 layers are separated and concentrated and the residue purified by prep TLC using 1:3 EtOAc:Hex to yield a colorless oil (0.91 g). Treat this oil with 10 % TFA in CH_2Cl_2 (5 ml) for 2 h, then concentrate to dryness. Suspend a portion of this material (0.026 g) in CH_2Cl_2, add 6-quinoline-carboxaldehyde (0.016 g) and $NaBH(OAc)_3$ (0.014 g). Stir the reaction overnight, then purify by prep TLC using EtOAc to give the title compound as a yellow oil. LCMS Rt 5.26min., observed mass 618.1 (M+H).

Using the same procedure as above but using piperonal in place of 6-quinoline-carboxaldehyde provides example 3a:



LCMS Rt 5.51min., observed mass 611.1(M+H)

Example 4



Step 1:

To CH_3Ph_3Br (13.58 g, 38 mmol, 2 eq) in THF (65 ml) at -78 ^{0}C was added n-BuLi (2.5 M in hexane, 15.2 ml, 2 eq) dropwise. The mixture was warmed to 0 ^{0}C and then cooled back to -78 ^{0}C before the ketone **11** (7 g, 1 eq)/30 ml THF) solution was transferred to the anion solution. 15 min later, the solution was warmed up to rt. After 1 h, the reaction was quenched by water. Extraction with ether and flash chromatography (EtOAc:Hexane, 1:6) gave the olefin **11f** as clear oil (6.7 g, 97 %). ^{1}HNMR ($CDCl_3$): δ 1.30 (m, 1 H), 1.41 (s, 9 H), 1.60 (m, 1 H), 1.80 (m, 2 H), 2.50 (m, 1 H), 2.75 (m, 2 H), 4.20 (, 2 H), 5.01 (s, 1 H), 5.20 (s, 1 H), 7.20 (d, 2 H, J = 8.3 Hz), 7.41 (d, 2 H, J = 8.3 Hz)

Step 2:

Hydroboration of the **11f** was done with 9-BBN and the alcohol was obtained in 97 % yield. ^{1}HNMR ($CDCl_3$): δ 1.00 (m, 1 H), 1.10-1.38 (m, 4 H), 1.40 (s, 9 H), 1.60-1.80 (m, 3 H), 2.40-2.60 (m, 2 H), 2.60-2.70 (m, 1 H), 3.60 (m, 2 H), 3.90-4.20 (m, 2 H), 7.00 (d, 2 H, J = 8.1 Hz), 7.40 (d, 2 H, J = 8.1 Hz).

The alcohol (0.63 g, 1.64 mmol, 1 eq) was stirred with NaH (60 %, 0.13 g, 2 eq), n-Bu_4NBr (0.2 g) in THF (5 ml) for 40 min before CH_3I (1 ml) was added. The mixture was stirred at 40 ^{0}C for 2 h. After extraction with EtOAc, flash chromatography (EtOAc:Hexane, 1:3) gave the methyl ether **11g** (0.45 g, 69 %).
^{1}HNMR ($CDCl_3$): δ 0.99 (m, 1 H), 1.10-1.38 (m, 4 H), 1.40 (s, 9 H), 1.60-1.80 (m, 3 H), 2.40-2.60 (m, 2 H), 2.60-2.70 (m, 1 H), 3.20 (s, 3 H), 3.60 (m, 2 H), 3.90-4.20 (m, 2 H), 7.00 (d, 2 H, J = 8.1 Hz), 7.40 (d, 2 H, J = 8.1 Hz).

Step 3:

11g (0.45 g, 1.13 mmol, 1 eq) was dissolved in THF (6 ml) and cooled to –78 ^{0}C under N_2. N-BuLi (2.5 M in hexane, 0.54 ml, 1.2 eq) was added dropwise and stirred for 5 min, then (R)-α-ethyl-4-chlorobenzylisocyanate (0.26 g, 1.2 eq) was added [Prepared from the amine (1 g, 5.90 mmol, 1 eq) by treatment with diphosgene (0.85 ml, 1.2 eq) and proton sponge (2.53 g, 2 eq) in 10 ml CH_2Cl_2). After 30 min, the crude was washed with 1 M HCl and 1 M NaOH. Flash chromatography (EtOAc:hexane,

1:5) provided 0.9 g of colorless liquid which was used immediately. ^{1}HNMR ($CDCl_3$): δ 1.00 (t, 3 H, J = 7.3 Hz), 1.80 (m, 2 H), 4.5 (t, 1 H, J = 7.3 Hz), 7.20 (d, 2 H, J = 8.3 Hz), 7.30 (d, 2 H, J = 8.3 Hz)]. The crude was stirred for –78 ^{0}C for 1 h and warmed up to rt for another hour. After quenching with water and extraction, flash chromatography (EtOAc:hexane, 1:3) provided **11h** (0.40 g, 69 %).

^{1}HNMR ($CDCl_3$): δ 1.00 (t, 3 H, J = 7.0 Hz), 1.10-1.25 (m, 2 H), 1.40 (s, 9 H), 1.60-1.90 (m, 4 H), 2.40-2.65 (m, 3 H), 3.22 (s, 3 H), 3.40 (m. 2 H), 3.80-4.20 (m, 2 H), 5.00 (q, 1 H, J = 7.2 Hz), 6.60 (d, 1 H, J =7.7 Hz), 7.20 (d, 2 H, J = 7.1 Hz), 7.25 (s, 4 H), 7.70 (d, 2 H, J = 7.0 Hz).

^{13}CNMR ($CDCl_3$): δ 12.12, 29.64, 30.28, 31.34, 31.59, 39.53, 52.43, 55.91, 60.15, 75.11, 80.44, 128.01, 129.06, 129.62, 129.69, 133.66, 133.88, 141.90, 147.50, 155.63, 167.68.

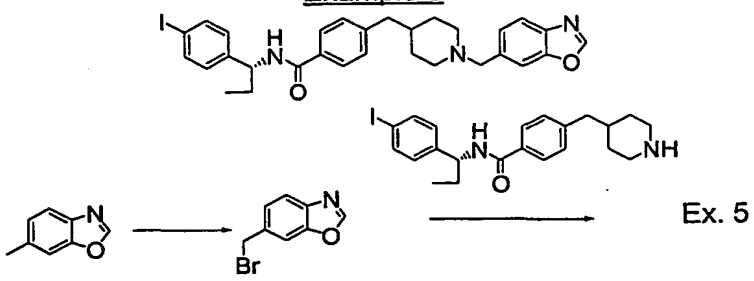
HRMS for $C_{29}H_{40}ClN_2O_4$ (M + 1) calcd: 262.0093; found: 262.0092.

Step 4:

11h (87 mg, 0.169 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.5 ml) and treated with 4 M HCl/dioxane (3 ml) for 24 h. The solvent was removed and the crude was basified with saturated $NaHCO_3$. Extraction with EtOAc provided 80 mg of the crude which was treated with 6-formylquinoline (80 mg, 3 eq) and $NaBH(OAc)_3$ (107 mg, 3 eq) in 5 ml CH_2Cl_2 for 24 h. The crude was washed with saturated Na_2CO_3 followed by extraction with CH_2Cl_2. Flash chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 98:2:1) provided 60 mg of the desired product **11i**.

^{1}HNMR ($CDCl_3$): δ 0.99 (t, 3 H, J = 7.3 Hz, 1.20 (m, 2 H), 1.40 (m, 1 H), 1.60 (m, 1 H), 1.90 (m, 4 H), 2.02 (m, 1 H), 2.60 (m, 1 H), 2.80 (d, 1 H, J = 12.1 Hz), 2.99 (d, 1 H, J = 11.7 Hz), 3.20 (s, 3 H), 3.60 (m, 2 H), 3.62 (s, 2 H), 5.00 (q, 1 H, J = 7.5 Hz), 6.58 (d, 1 H, J = 7.9 Hz), 7.20 (d, 2 H, J = 8.3 Hz), 7.22 (m, 3 H), 7.38 (m, 1 H), 7.70 (m, 4 H), 8.00 (d, 1 H, J = 8.0 Hz), 8.10 (d, 1 H, J = 8.3 Hz), 8.90 (d,1 H, J = 4.0 Hz)

Example 5



6-Methylbenzoxazole was reacted with NBS (1 eq) and catalytic amount of benzoyl peroxide in CCl_4 at 90 ^{0}C for 12 h to obtain 6-bromomethylbenzoxazole which was purified by flash chromatography (EtOAc:Hexane = 1:5).

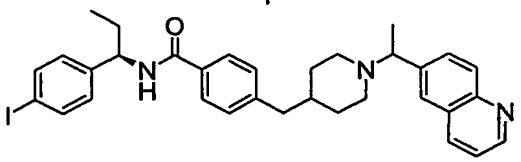
^{1}HNMR ($CDCl_3$): δ 4.60 (s, 2 H), 7.42 (d, 1 H, J = 8.2 Hz), 7.64 (s, 1 H), 7.76 (d, 1 H, J = 8.2 Hz), 8.12 (s, 1 H). The product (42 mg, 1.5 eq) was immediately reacted with

the piperidine derivative (62 mg, 1 eq) with K_2CO_3 in CH_3CN (3 ml) at 80 °C under N_2 overnight. Direct chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 98:2:1) gave the desired product (8.4 mg).

^{1}HNMR ($CDCl_3$): δ 1.00 (t, 3 H, J = 7.3 Hz), 1.20-1.40 (m, 2 H), 1.50-1.70 (m, 3 H), 1.80-2.00 (m, 4 H), 2.60 (d, 2 H, J = 6.6 Hz), 2.90 (d, 2 H, J = 10.5 Hz), 3.60 (s, 2 H), 5.00 (q, 1 H, J = 7.6 Hz), 6.38 (d, 1 H, J = 7.9 Hz), 7.05 (d, 2 H, J = 8.2 Hz), 7.19 (d, 2 H, J = 8.1 Hz), 7.30 (d, 1 H, J = 8.1 Hz), 7.60 (s, 1 H), 7.62-7.70 (dm, 5 H).

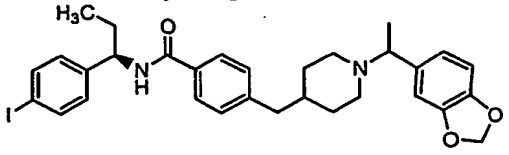
HRMS for $C_{30}H_{33}IN_3O_2$ (M + 1) calcd: 594.1618; found: 594.1612.

Example 6



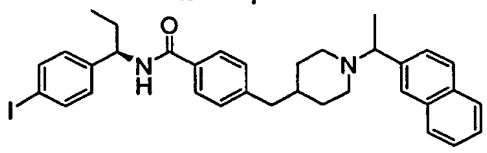
Compound **14** (150 mg, 0.325 mmol) is dissolved in dry CH_2Cl_2 under N_2, Ti(Oi-Pr)$_4$ (0.144 ml, 0.487 mmol) and quinoline-6-carboxaldehyde (77 mg, 0.487 mmol) are added and stirred overnight. the reaction is cooled to 0 °C under N_2, CH_3MgBr (0.325 ml of 3M solution, 0.975 mmol) is added dropwise, THF (1 ml) is added, and the reaction is stirred for 4 h. The reaction is quenched with water, and EtOAc and 1N NaOH are added. The mixture is filtered through celite, the organic layer is separated and washed with sat. NaCl, dried over Na_2SO_4, and purified by flash chromatography with CH_2Cl_2/2N NH_3 in CH_3OH (97/3) to obtain the title compound. LCMS Rt 7.06 min., observed mass 618.1 (M+H).

Using the same procedure, but with piperonal in place of quinoline-6-carboxaldehyde, gives Example 6a:



LCMS Rt 5.01 min., 611.1 obs. mass (M+H)

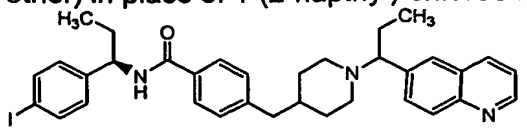
Example 7



14 (100 mg, 0.22 mmol) and 1-(2-napthyl)-chloroethane (63 mg, 0.33 mmol) are suspended in 4-methyl-2-pentanone (3 ml). Na_2CO_3 (466 mg, 4.4 mmol) and KI (4.0 mg, 0.022 mmol) are added into the above mixture, and the sealed tube is heated at 80 °C overnight. The reaction mixture is cooled tort, filtered and washed with CH_2Cl_2, the CH_2Cl_2 solution is concentrated and purified by flash chromatography with

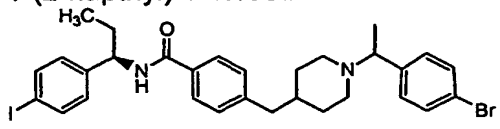
CH_2Cl_2/2N NH_3 in CH_3OH (97:3) to yield the title compound. LCMS Rt 5.51 min., observed mass 617.1 (M+H).

Use the same procedure, but with 6-(1-[methylsulfonyloxy]propyl)-quinoline (prepared from the corresponding alcohol by reaction with CH_3SO_2Cl and DIPEA in ether) in place of 1-(2-napthyl)-chloroethane to obtain Example 7a:



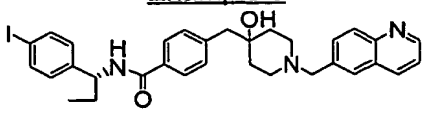
LCMS Rt 5.16 min. 632.1 obs. mass (M+H)

Use the same procedure but with 1-(4-bromophenyl)-chloroethane in place of 1-(2-napthyl)-chloroethane to obtain Example 7b:



LCMS Rt 5.23 min. obs. mass 647.2 (M+H)

Example 8



Step 1:

To **15** (10.1 g, 20.14 mmol, 1 eq)/90 ml anhydrous THF was added KHMDS (0.5 M, 44 ml, 1.1 eq) at rt under N_2. After stirring for 1 h, the ketone (see Scheme 5) (4.8 g, 1.2 eq) was added and the mixture was heated to 90 ^{0}C for 24 h. The reaction was quenched by water and extracted with EtOAc. The organic layer was dried with $MgSO_4$ and flash chromatography (EtOAc:hexane, 1:10) afforded **15a** as white solid (4.15 g, 62 % yield).

^{1}HNMR ($CDCl_3$): δ 1.40 (s, 9 H), 2.38 (m, 2 H), 2.42 (m, 2 H), 3.40 (m, 2 H), 3.70 (m, 2 H), 3.90 (s, 3 H), 6.40 (s, 1 H), 7.20 (d, 2 H, J = 8.3 Hz), 8.00 (d, 2 H, J = 8.3 Hz).

Step 2:

Intermediate **15a** (0.9 g, 2.72 mmol, 1 eq) was dissolved in CH_2Cl_2 (10 ml) at rt and MCPBA (1.87 g, 50 %, 2 eq) for 24 h. 10 % Na_2SO_3 (10 ml) was added and the organic layer was further washed with $NaHCO_3$. After drying with $MgSO_4$, the solvent was removed and the residue redissolved in CH_3OH. Pd/C (0.1 g) was added the reaction was conducted under H_2 balloon at rt for 3 h. After filtration through celite, flash chromatography (EtOAc:hexane, 1:1) provided **15b** as white solid (0.59 g, 56 % yield).

^{1}HNMR ($CDCl_3$): δ 1.30-1.60 (m, 4 H), 1.40 (s, 9 H), 2.78 (s, 2 H), 3.00-3.16 (m. 2 H), 3.70-3.90 (m, 2 H), 3.88 (s, 3 H), 7.20 (d, 2 H, J = 8.2 Hz), 7.90 (d, 2 H, J = 8.2 Hz).

^{13}CNMR ($CDCl_3$): δ 29.64, 29.69, 30.28, 37.84, 50.49, 53.23, 70.70, 80.57, 129.52, 130.43, 131.55, 142.83, 155.69, 167.88.

HRMS for $C_{19}H_{28}NO_5$ (M + 1) calcd: 350.1967; found: 350.1968.

Step 3:

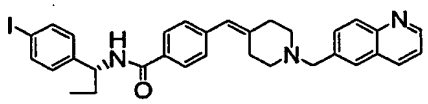
15b (0.56 g, 0.968 mmol, 1 eq) was stirred with $LiOH \cdot H_2O$ (40 mg) in THF (2 ml), CH_3OH (2 ml) and H_2O (2 ml) at 40 ^{0}C for 20 h. The solvent was removed and the solution was treated with concentrated HCl to pH 1. Extraction with CH_2Cl_2 afforded 0.45 g acid in 84 % yield.

^{1}HNMR ($CDCl_3$): δ 1.40-1.65 (m, 4 H), 1.42 (s, 9 H), 2.80 (s, 2 H), 3.00-3.20 (m. 2 H), 3.80-3.95 (m, 2 H), 3.88 (s, 3 H), 7.30 (d, 2 H, J = 8.2 Hz), 8.00 (d, 2 H, J = 8.2 Hz).

The acid (215 mg, 0.371 mmol, 1 eq) was mixed with R-α-ethyl-4-iodo-benzylamine (97 mg, 1 eq), HATU (142 mg, 1 eq), Hunig's base (0.14 ml, 2 eq) in 1 ml of DMF and stirred for 1.5 h. The crude was extracted with EtOAc and dried over $MgSO_4$. After removal of the solvent, the crude was treated with 4M HCl/dioxane (2 ml) for 5 h. The solvent was removed and basified with saturated Na_2CO_3. Extraction with CH_2Cl_2 several times and then removal of the solvent provided the desired product. It was then immediately treated with 6-formylquinoline (65 mg, 1.1 eq) and $NaBH(OAc)_3$ (89 mg, 1.1 eq) in CH_2Cl_2 (5 ml) for 39 h. The crude was washed with saturated Na_2CO_3 followed by extraction with CH_2Cl_2. Flash chromatography (CH_2Cl_2: CH_3OH:NH_4OH, 98:2:1) provided 39 mg of the title compound in 23 % yield.

^{1}HNMR ($CDCl_3$): δ 0.98 (t, 3 H, J = 7.4 Hz), 1.30 (br s, 1 H), 1.50 (d, 2 H, J = 13.2 Hz), 1.70-1.80 (m, 2 H), 1.80-2.00 (m, 2 H), 2.35 (t, 2 H, J = 10.9 Hz), 2.62 (d, 2 H, J = 11.2 Hz), 2.80 (s, 2 H), 3.62 (s, 2 H), 5.00 (q, 1 H, J = 7.5 Hz), 6.30 (d, 1 H, J = 7.6 Hz), 7.05 (d, 2 H, J = 8.2 Hz), 7.24 (d, 2 H, J = 7.6 Hz), 7.40 (dd, 1 H, J = 4.2, 8.2 Hz), 7.60-7.77 (m, 6 H), 8.02 (d, 1 H, J = 9.1 Hz), 8.10 (d, 1 H, J = 8.8 Hz), 8.90 (d, 1 H, J = 4.1 Hz). HRMS for $C_{32}H_{35}IN_3O_2$ (M + 1) calcd: 620.1774; found: 620.1769.

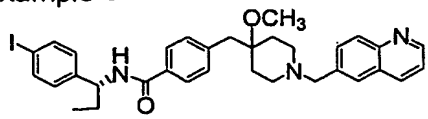
Using the procedure in step 3 with **15a** as starting material, Example 8A was obtained:



^{1}HNMR ($CDCl_3$): δ 0.99 (t, 3 H, J = 7.2 Hz), 1.80-1.90 (m, 2 H), 2.40-2.70 (m, 8 H), 3.73 (s, 2 H), 5.00 (q, 1 H, J = 7.2 Hz), 6.29 (s, 1 H), 6.32 (d, 1 H, J = 8.0 Hz), 7.09 (d, 2 H, J = 8.0 Hz), 7.20 (d, 2 H, J = 8.2 Hz), 7.40 (dd, 1 H, J = 4.4, 8.3 Hz), 7.65 (d, 2 H, J = 8.3 Hz), 7.69 (d, 2 H, J = 8.0 Hz); 7.76 (d, 1 H, J = 7.2 Hz), 8.07 (d, 1 H, J = 8.8 Hz), 8.13 (d, 1 H, J = 8.0 Hz), 8.88 (d, 1 H, J = 4.0 Hz).

HRMS for $C_{32}H_{33}IN_3O$ (M + 1): calcd: 602.1668; found: 602.1657.

The compound of Example 8B



was prepared from the tertiary alcohol **15b** (0.19 g, 0.54 mmol, 1 eq) by dissolving in anhydrous THF (5 ml) and treating with NaH (60 %, 0.2 g, 10 eq) and CH_3I (1 ml). The mixture was stirred at rt overnight. After quenching the reaction with CH_3OH, the solvent was removed and extraction with CH_2Cl_2 followed by flash chromatography (EtOAc:Hexane, 1:3) provided the desired methyl ether (46 mg, 23 %).

^{1}HNMR ($CDCl_3$): δ 1.42 (s, 9 H), 1.35-1.50 (m, 2 H), 1.60-1.70 (m, 2 H), 2.80 (s, 2 H), 2.90-3.10 (m, 2 H), 3.38 (s, 3 H), 3.70-3.85 (m, 2 H), 3.90 (s, 3 H), 7.20 (d, 2 H, J = 8.1 Hz), 7.99 (d, 2 H, J = 8.1 Hz).

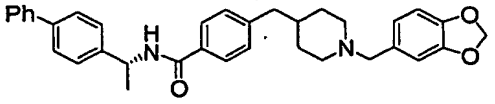
The methyl ether was treated with $LiOH{\cdot}H_2O$ (58 mg) in 1 ml water/0.5 ml THF/0.5 ml CH_3OH at 40 ^{0}C for 60 h. The solvent was removed and the pH was adjusted to 1. Extraction with EtOAc and drying over $MgSO_4$ gave the corresponding acid (45 mg).

^{1}HNMR ($CDCl_3$): δ 1.42 (s, 9 H), 1.40-1.50 (m, 2 H), 1.60-1.70 (m, 2 H), 2.80 (s, 2 H), 2.90-3.10 (m, 2 H), 3.40 (s, 3 H), 3.70-3.85 (m, 2 H), 7.20 (d, 2 H, J = 8.1 Hz), 8.02 (d, 2 H, J = 8.1 Hz).

The acid (45 mg) was treated with R-α-ethyl-4-iodo-benzylamine (37 mg, 1.1 eq), HATU (49 mg, 1 eq) and 2 eq of Hunig's base in 0.5 ml DMF for 24 h. After workup, 74 mg of the crude was obtained. The material was dissolved in 4 M HCl/dioxane (2 ml) and stirred overnight. After removal of the solvent, the crude was basified to pH 10 and extracted with EtOAc. About one half of the obtained product (30 mg, 0.061 mmol) was treated with 6-formylquinoline (76 mg, 8 eq) and $NaBH(OAc)_3$ (103 mg, 8 eq) in 4 ml CH_2Cl_2 for 22 h. The crude was washed with saturated Na_2CO_3 followed by extraction with CH_2Cl_2. Flash chromatography (CH_2Cl_2: CH_3OH:NH_4OH, 98:2:1) provided 32 mg of the title compound.

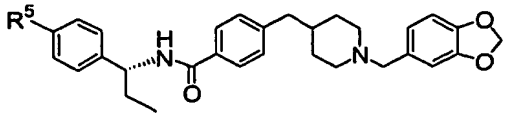
^{1}HNMR ($CDCl_3$): δ 0.98 (t, 3 H, J = 7.3 Hz), 1.50-1.70 (m, 4 H), 1.80-1.90 (m, 2 H), 2.2-2.00-2.40 (m, 2 H), 2.55-2.70 (m, 2 H), 2.78 (s, 2 H), 3.30 (s, 3 H), 3.70 (s, 2 H), 4.90 (s, 1 H), 5.00 (q, 1 H, J = 7.3 Hz), 6.40 (d, 1 H, J = 8.0 Hz), 7.05 (d, 2 H, J = 8.1 Hz), 7.18 (d, 2 H, J = 8.0 Hz), 7.40 (m, 1 H), 7.60-7.80 (m, 5 H), 8.02 (m, 1 H), 8.10 (d, 1 H, J = 8.0 Hz), 8.95 (m, 1 H).

Example 9

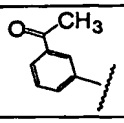
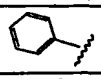
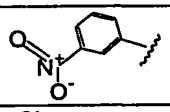
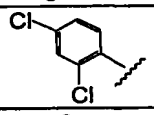
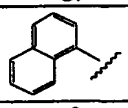
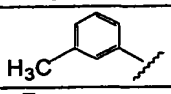
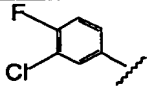
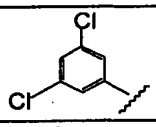
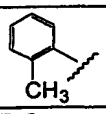
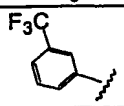
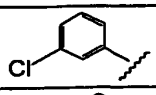
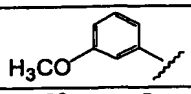
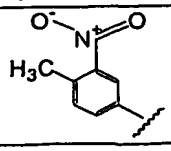


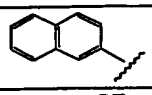
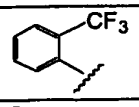
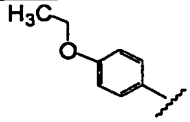
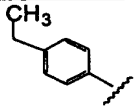
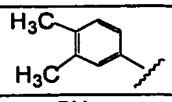
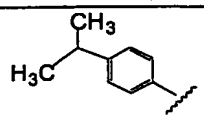
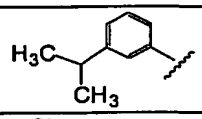
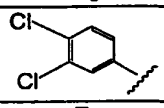
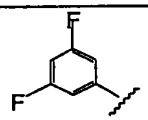
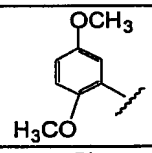
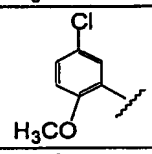
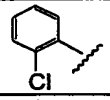
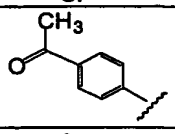
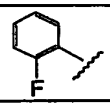
The iodide analog on the Argopore-MB-CHO resin (prepared as described in the general synthesis procedures, 100 mg, 0.7 mmol/g, 0.07 mmol) was mixed with phenylboronic acid (42 mg), $Pd(PPh_3)_4$ (8 mg), K_2CO_3 (100 mg) in 0.5 ml DMF. The mixture was stirred under Ar at 40 ^{0}C for 12 h. The crude was washed with 5 % KCN/DMF, water, CH_3OH, CH_2Cl_2, and the final product was cleaved with 10 % TFA/ CH_2Cl_2 and dried as TFA salt. LC-MS Rt 4.83 min., observed mass 533 (M + H).

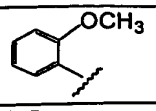
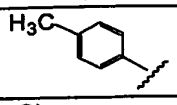
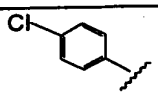
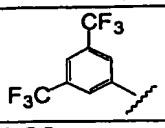
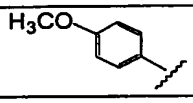
Using this procedure and the appropriate aromatic halides the examples in Table 3 of the formula



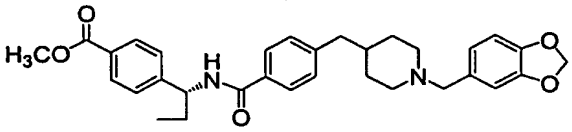
wherein R5 is defined in the table, were prepared.

Ex.	R^5	Rt(min)	Obs. Mass (m+H)
9-1		4.36	589
9-2		4.61	547
9-3		4.56	592
9-4		5.26	615
9-5		5.06	597
9-6		4.86	561
9-7		4.96	599
9-8		5.46	615
9-9		4.86	561
9-10		5.01	615
9-11		4.96	581
9-12		4.61	577
9-13		4.76	606

9-14		5.16	597
9-15		4.86	615
9-16		4.86	591
9-17		5.16	575
9-18		5.16	575
9-19		5.46	589
9-20		5.36	589
9-21		5.31	615
9-22		4.81	583
9-23		4.56	607
9-24		4.96	611
9-25		4.86	581
9-26		4.36	589
9-27		4.71	565

9-28		4.71	577
9-29		4.96	561
9-30		5.06	581
9-31		5.36	683
9-32		4.66	577

Example 10



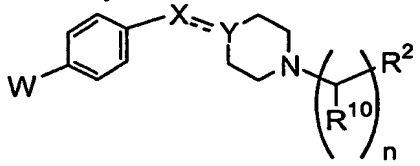
The iodide analog on the Argopore-MB-CHO resin (100 mg, 0.7 mmol/g, 0.07 mmol) was mixed with $Pd(OAc)_2$ (50 mg), Et_3N (0.2 ml) and Ph_3P (0.1 g) in CH_3OH (10 ml). The mixture was stirred under CO atmosphere at 50 ^{0}C for 12 h. The crude was washed with water, CH_3OH, CH_2Cl_2 and the final product was cleaved with 10 % TFA/ CH_2Cl_2 and dried as TFA salt. Flash chromatography (CH_2Cl_2:CH_3OH:NH_4OH, 98:2:1) gave the desired product (19 mg).

^{1}HNMR ($CDCl_3$): δ 1.00 (t, 3 H, J = 7.4 Hz), 1.30 (m, 2 H), 1.50 (m, 3 H), 1.70-2.00 (m, 4 H), 2.58 (d, 2 H, J = 6.8 Hz), 2.90 (d, 2 H, J = 11.5 Hz), 3.40 (s, 2 H), 3.90 (s, 3 H), 5.10 (q, 1 H, J = 7.6 Hz), 5.99 (s, 2 H), 6.40 (d, 1 H, J = 7.8 Hz), 6.70 (s, 2 H), 6.80 (s, 1 H), 7.20 (d, 2 H, J = 8.2 Hz), 7.40 (d, 2 H, J = 8.3 Hz), 7.66 (d, 2 H, J = 8.3 Hz), 8.00 (d, 2 H, J = 8.3 Hz).

LC-MS Rt 4.36 min., observed mass 528 (M + H).

WHAT IS CLAIMED:

1. Compounds represented by the structural formula



I

or a pharmaceutically acceptable salt, ester or solvate thereof, wherein

W is R^1-$CR^3R^{12}NR^4C(O)$- or $R^{11}C(O)NR^4$-;

the dotted line is an optional double bond;

X is $-CHR^8$-, -C(O)-, -C(=NOR^9)-, or, when the double bond is present, -CR^8=;

Y is

$-\overset{|}{C}H-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_1\text{-}C_4\text{alkoxy})-$, or, when the double bond is present, $-\overset{\|}{C}-$;

R^1 is R^5-$(C_3\text{-}C_8)$cycloalkyl, R^5-$(C_3\text{-}C_8)$cycloalkyl$(C_1\text{-}C_6)$alkyl, R^5-aryl, R^5-aryl-$(C_1\text{-}C_6)$alkyl, R^5-heteroaryl, R^5-heteroaryl$(C_1\text{-}C_6)$alkyl, R^5-heterocycloalkyl or R^5-heterocycloalkyl$(C_1\text{-}C_6)$alkyl;

R^2 is R^6-aryl or R^6-heteroaryl;

n is 1, 2 or 3;

R^3 is $C_1\text{-}C_6$ alkyl, aryl or heteroaryl;

R^4 is H or $C_1\text{-}C_6$ alkyl;

R^5 is 1-4 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, $C_1\text{-}C_6$ alkoxy, $-CF_3$, $(C_1\text{-}C_6)$-alkoxycarbonyl, $-SO_2NHR^4$, -C(O)NHR^4, $-NR^4C(O)NHR^4$, $-NR^4C(O)R^4$, $-NR^4SO_2R^4$, R^{13}-phenyl and naphthyl;

R^6 is 1-4 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, -SH, -S($C_1\text{-}C_6$ alkyl), -CN, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkylcarboxy, CF_3, $-NO_2$, $-NH_2$, $(C_1\text{-}C_6)$alkylamino, phenyl, $(C_1\text{-}C_6)$-alkoxycarbonyl and R^7-phenoxy, or adjacent ring carbon atoms form a ring with the group $-O(CH_2)_{1\text{-}2}O$-, $-O(CH_2)_{2\text{-}3}$- or $-O(CF_2)O$-;

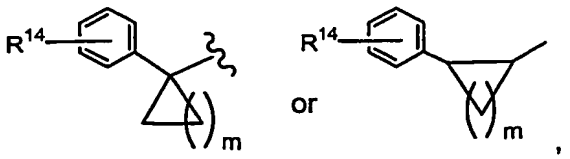
R^7 is 1-3 substituents independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl, halogen, -OH, $C_1\text{-}C_6$ alkoxy and CF_3;

R^8 is H, $C_1\text{-}C_6$ alkyl or $(C_1\text{-}C_4)$alkoxy-$(C_1\text{-}C_4)$alkyl;

R^9 is H, $C_1\text{-}C_6$ alkyl or aryl-$(C_1\text{-}C_4)$alkyl;

R^{10} is independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl and aryl;

R^{11} is



,

or, when R^2 is R^6-heteroaryl or R^{10} is not H, R^{11} can also be R^5-phenyl(C_0-C_2)alkyl;

m is 1, 2, 3, 4 or 5;

R^{12} is H or C_1-C_6 alkyl;

R^{13} is 1 to 3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, -OH, C_1-C_6 alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$ and $-C(O)CH_3$; and

R^{14} is 1-3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, -OH, C_1-C_6 alkoxy and CF_3.

2. A compound of claim 1 wherein W is R^1-$CR^3R^{12}NR^4C(O)$-.

3. A compound of claim 2 wherein R^1 is R^5-phenyl.

4. A compound of claim 1 wherein R^2 is R^6-aryl.

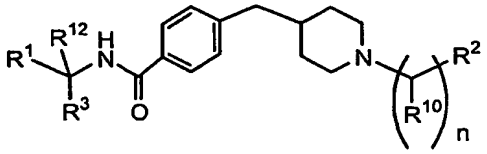
5. A compound of claim 5 wherein R^{10} is H and n is 1.

6. A compound of claim 1 wherein X is $-CHR^8$ and Y is CH.

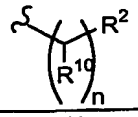
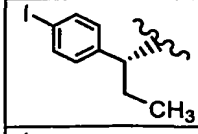
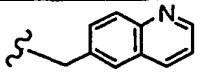
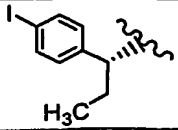
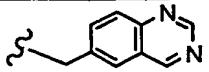
7. A compound of claim 1 wherein X and Y form a double bond.

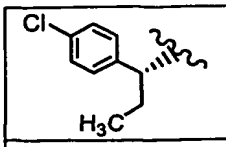
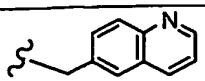
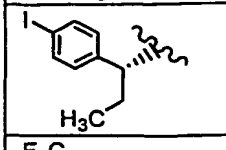
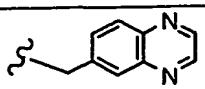
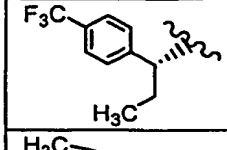
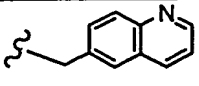
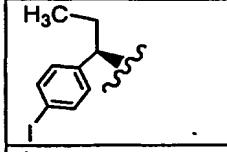
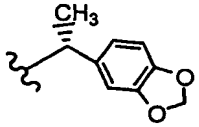
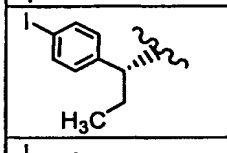
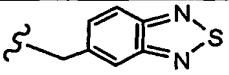
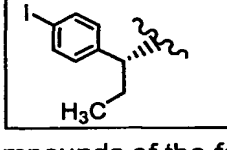
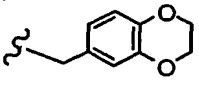
8. A compound of claim 1 selected from the group consisting of:

compounds of the formula



wherein

R^1-$CR^{12}R^3$-	
	
	

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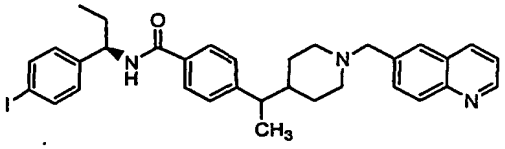
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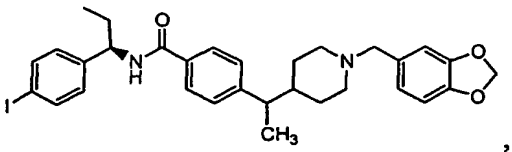
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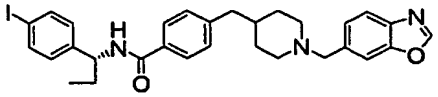
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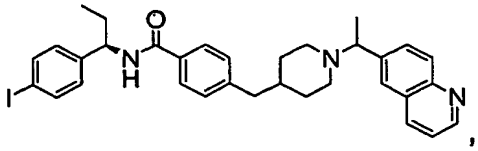
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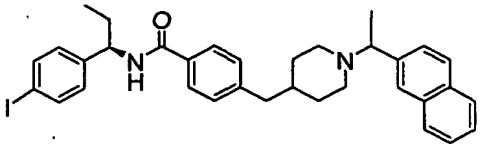
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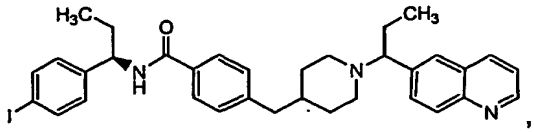
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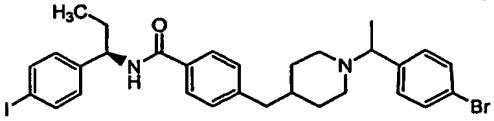
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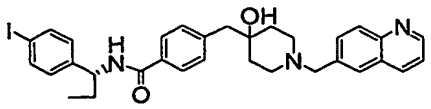
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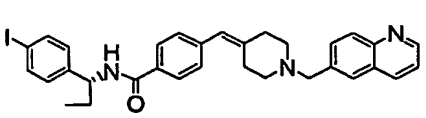
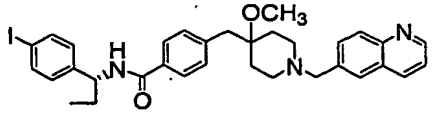
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9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

10. The use of a compound of claim 1 for the preparation of a medicament for treating an eating disorder or diabetes.

INTERNATIONAL SEARCH REPORT

mational Application No
PCT/US 01/49301

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/34 C07D401/06 C07D405/06 C07D413/06 C07D417/06
A61K31/41 A61K31/42 A61K31/425 A61K31/445 A61K31/47
A61K31/495 A61K31/505 A61P3/04 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K .

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 00367 A (NOVONORDISK AS) 7 January 1999 (1999-01-07) page 1, line 11 - line 15; claim 1	1-10
A	EP 0 643 057 A (SQUIBB BRISTOL MYERS CO) 15 March 1995 (1995-03-15) page 24, line 28 - line 32; claim 1; examples 1,20,256,261,262	1-10
P,A	WO 01 09137 A (OHSHIMA ETSUO ;SONE HIROKI (JP); KOTERA OSAMU (JP); KYOWA HAKKO KO) 8 February 2001 (2001-02-08) page 7, line 15 - line 32; claim 33 page 29, line 15 - line 19	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2002	22/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hanisch, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

rnational Application No
PCT/US 01/49301

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